Deep Brain Stimulation for Psychiatric Disorders

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Summary: Surgery for psychiatric disorders first began in the early part of the last century when the therapeutic options for these patients were limited. The introduction of deep brain stimulation (DBS) has caused a new interest in the surgical treatment of these disorders. DBS may have some advantage over lesioning procedures used in the past. A critical review of the major DBS targets under investigation for Tourette's syndrome, obsessive-compulsive disorder, and major depression is presented. Current and future challenges for the use of DBS in psychiatric disorders are discussed, as well as a rationale for referring to this subspecialty as limbic disorders surgery based on the parallels with movement disorders surgery. **Key Words:** Deep brain stimulation, Tourette's syndrome, obsessive-compulsive disorder, major depression, treatment-resistant depression, psychosurgery.

INTRODUCTION

Perhaps no other word in the field of neurosurgery, or medicine for that matter, conjures up a more negative connotation than the word "psychosurgery." Although the history of this discipline may lead some to conclude that its reputation is somewhat justified, the current era of functional neurosurgery is providing new opportunities for scientific advances in the surgical treatment of psychiatric disorders, as well as a set of new challenges. With thoughtful, methodical approaches to clinical trial construction, surgical technique, and the sharing of meaningful data, psychosurgery may well end up being one of the most important and well-respected specialties of the new century.

To understand the current work being done and where these efforts may go in the future, it is important to understand the history of psychosurgery. Although reports of neurosurgical procedures for derangements in behavior and thinking date back to the late 1800s, the earliest formal series of procedures specifically aimed at the treatment of psychiatric disorders were performed in the mid 1930s. Egas Moniz, a Portuguese neurologist, and Almeida Lima, a neurosurgeon, performed a series of frontal leucotomies starting in November of 1935 after hearing a lecture on frontal lobe function and anxiety states in primates. In his subsequent publications describing these procedures, Moniz was the first to coin the term "psychosurgery."[1] Shortly thereafter, American neurologist Walter Freeman and a neurosurgical colleague, James Watts, started performing a similar procedure in 1936, which they renamed the "frontal lobotomy" later that year.

Although there was immediate skepticism and alarm by many at the time, it is important to understand the context in which these events occurred. In the 1930s, the field of psychiatry was young and deeply divided between those who believed that psychiatric disease was a disorder of thought best treated with psychoanalysis, and those who believed such diseases were biological disorders of the brain. More importantly, this was before the advent of chlorpromazine or any psychiatric medications. The only treatment options were institutionalization and the so-called "shock therapies" using insulin (pentetrazol) or electricity. This lack of effective treatment, in combination with the ever-growing numbers of patients, caused a dramatic rise in the number of psychiatric inpatients in the 1920s and 1930s. By 1939, there were 480,000 psychiatric hospital beds in the United States, more than both the medical and surgical hospital beds combined at the time. Many physicians were happy to pursue any therapy that might successfully treat these disorders.[2]

Although these early procedures were imprecise and barbaric by today's standards, many of the early practitioners of psychosurgery were not always as reckless as history remembers them. The earliest work by Moniz and Freeman was based on primate experiments in frontal

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disconnection done at Yale by John Fulton and Carlyle Jacobsen. Freeman and Watts sought and developed specific instruments and practiced the procedure on a cadaver first. Freeman almost obsessively followed-up with his patients for years, even decades, after their procedures. Some of the greatest neurosurgical names of the day performed the procedures at one time or another. Freeman himself was extremely active in organized medicine and actively presented and published his work. His downfall, and thus the downfall of the lobotomy, was due in large part to his failure to objectively evaluate the place surgery had in the treatment of psychiatric disorders after the introduction of chlorpromazine, and his increasingly overzealous advocacy of the procedure.[2]

With the development of human stereotactic techniques by Spiegel and Wycis in the 1940s and later with the introduction of computed tomography and MRI, our ability to accurately and discretely place lesions in the brain significantly improved. The establishment of clinical definitions of the various psychiatric disorders and the development of clinical rating scales for the disorders gave investigators the substrate by which to objectively evaluate and compare treatment outcomes. The development of deep brain stimulation (DBS) in the 1990s led to a renewed interest in the surgical treatment of psychiatric disorders.

DBS is perceived as having an advantage over prior surgical procedures that carry the stigma of lesioning targets in the brain permanently. DBS is adjustable, with multiple stimulation parameters that can be manipulated by the practitioner including amplitude, frequency, and width of the stimulating pulse, and to a lesser extent the location and shape of the stimulating field. In addition, it is nondestructive and reversible, meaning that the presence of the electrode itself in the brain does not disrupt the normal brain circuitry, and when the stimulator is off, it is in essence "not there." The latter provides the potential for more rigorous clinical trials with subjects and evaluators blinded to the stimulation condition, something that is impossible to accomplish with lesioning procedures unless a placebo-controlled sham trial is used. Although these points are valid, and DBS may confer therapeutic advantages at the level of the brain, it remains to be seen whether it really represents an advantage to the patient. Hardware complications, such as lead fracture, infection, patient compliance issues (e.g., basic wound care problems at best, self mutilation of the implanted device at worst), and in some cases the need for very frequent battery changes, are all potential disadvantages of DBS over lesioning procedures.[3–8]

The three psychiatric disorders currently under investigation with DBS are Tourette's syndrome (TS), obsessive-compulsive disorder (OCD), and treatment-resistant depression (TRD). All three have a history of being successfully treated with lesioning procedures in various targets, making them a logical place to start. This is analogous to the early adoption of DBS in movement disorders, where thalamotomy and pallidotomy were replaced by thalamic and pallidal stimulation. It was apparent as far back as Moniz's original series of limbic leucotomy that the psychotic disorders did not respond well to the lesioning procedures, and this has held true, by and large, since that time. There are no studies in the use of DBS for schizophrenia currently underway.

The selection of targets for DBS is perhaps one of the greatest challenges in treating psychiatric disorders with this modality. The treatment of Parkinson's disease benefited from a widely used, although imperfect, primate model that has produced a reasonable and predictive model for the possible neuronal circuitry underlying the disorder. This model supported the use of some targets for DBS (such as the pallidum) and led to the discovery of others (such as the subthalamic nucleus and pedunculopontine nucleus).[9–11] There is not yet a well-validated animal model for any of the psychiatric disorders, although efforts are underway.[12,13] As a result, target selection to date has been largely based on prior lesioning experience. However, functional neuroimaging and fortuitous discoveries while using DBS to treat other conditions have also led to trials of new targets, and these may play a larger role as the discipline moves forward.

What follows is a brief overview of some of the work being done in each of these disorders in the current era. This is not meant to be an encyclopedic catalogue of every target that has been explored for DBS in psychosurgery, but rather a highlight of what are considered to be some of the major candidate brain targets for each disorder. One must keep in mind that many of these are either single case reports or small series, some in unblinded or less than optimally blinded conditions. Therefore, the results must be considered in this context.

For each of the disorders reviewed, I have included an accompanying table to outline the available information regarding stimulation parameters. For the sake of space, only the patients that were considered responders from each trial are included. The stereotactic coordinates are given relative to the anterior commissure (AC), the posterior commissure (PC), or the midpoint between the two (midcommissural point [MCP]). All coordinates are given relative to the midcommissural point unless otherwise noted. The stimulation mode and the number of active contacts are given, where the internal pulse generator is referred to as the case (C), and each contact is referred to as 0, 1, 2, and 3 (0 being most ventral) with the appropriate sign for assignment of cathode (-) and anode (+). Finally, the amplitude in volts (v), pulse width (PW) in microseconds, and frequency in hertz (Hz) are shown.

TABLE 1. *Stimulation Parameters for Reviewed Studies in Tourette's Syndrome*

Target	Author	AC-PC Coordinates	Patient	Side	Contacts	Amp (v)	PW (microsec)	Frequency (Hz)
Medial Thalamus (Spv, Ce, Voi)	Vandewalle et al. [3]	Lat = 5 AP = -4 Vert = 0	1	R*	0- 1- 2+ 3+	2.4	210	100
				L†	0- 1- 2+ 3+	2.2	210	100
			2	R†	2- 3- C+	3	210	65
				L†	3- C+	2.8	210	65
			3	R†	1- C+	2.8	210	100
				L*	2- C+	2.4	210	100
	Ackermans et al. [18]	Lat = 5 AP = - 4 Vert = 0	2	R	0- 1- C+	6.4	120	130
				L	0- 1- C+	6.4	120	130
Medial Thalamus (Ce-Pf)	Houeto et al. [4]	Lat = 6.1‡ AP = 2.9‡§ Vert = 1.9‡	1	R	0- 1- C+	1.5	60	130
				L	0- 1- C+	1.5	60	130
Limbic GPi	Houeto et al. [4]	Lat = 11.2‖ AP = 22.1§‖ Vert = -3.7‖	1	R	0- C+	1.5	60	130
				L	0- C+	1.5	60	130
Motor GPi	Diederich et al. [17]	Lat = 17 AP = 4 Vert = -5	1	R	0- 1+	2	120	185
				L	0- 1+	2	150	185
	Ackermans et al. [18]	Lat = 21.5 AP = 4 Vert = -3	1	R	0- 1- 2- C+	3.1	210	170
				L	0- 1- 2- C+	3.1	210	170

AC = anterior commissure; AP = anterior-posterior; Ce = centromedian nucleus; GPi = globus pallidus internus; L = left; Lat = lateral; MCP = midcommissural point; PC = posterior commissure; Pf = parafascicular nucleus; PW = pulse width; R = right; SPV = substantia periventricularis; v = volts; Vert = vertical; Voi = nucleus ventrooralis internus.
*Implanted 2-mm medial to original target, contact 1 placed at target depth. †Contact 1 placed at target. ‡Reported as "location of therapeutic contacts 0 and 1." §Given relative to PC, not MCP. ‖Reported as "location of therapeutic contact 0."

TOURETTE'S SYNDROME

The natural history of this childhood onset, neurodevelopmental disorder is marked by the development of characteristic vocal and/or motor tics that either subside or resolve completely by the late teens or early twenties. However, in a significant number of patients, tics may persist into adulthood. Treatment with neuroleptics and newer antipsychotic medications may not be effective, and their use can lead to the development of tardive dyskinesia. As is common with psychiatric disorders, there are frequent comorbidities, and TS is commonly associated with OCD and attention deficit hyperactivity disorder (ADHD).

The most frequently implanted target for TS in the literature is the medial thalamus. The best known work to date was a series of three patients, published in 2003 by a Dutch-Flemish group.[3] Medtronic model 3387 DBS leads (Medtronic, Minneapolis, MN) were placed bilaterally, using a trajectory that placed the electrode array across the nucleus ventrooralis internus (Voi), centromedian nucleus (Ce), and the substantia periventricularis (Spv). This selection of target trajectory was meticulously based on historical lesioning studies performed by Hassler and Dieckmann[14–16] decades earlier. The stimulation parameters are shown in Table 1. The three patients, with long-term follow-ups of 8 months, 1 year, and 5 years, showed a striking reduction in the number of tics per 10-minute period of 86.2%, 72.2%, and 90.1%, respectively. Evaluators were blinded to the stimulation condition, but patients were not. Side effects included a feeling of reduced energy at amplitudes that produced the best tic reduction in all three patients, and alterations in sexual function in two patients. Two of the three patients required multiple revisions of the pulse generator and lead extension due to traction pain. When examining the active lead locations used in these patients, it appeared that the more ventral contacts (i.e., those in the vicinity of Ce and Spv) provided the most efficacy, an observation that has also been made in subsequent patients (Larson, personal communication). Other large series in North America and Italy using the medial thalamus are either underway or awaiting publication.

The globus pallidus internus (GPi) has also been proposed as a target for TS. The pallidum, like other basal ganglia nuclei, has subterritories that appear to subserve motor, limbic, and associative information. The rationale for using the GPi in TS was that stimulation of the motor territory of this target helps relieve hyperkinetic states, such as dystonia and the dyskinesias of Parkinson's disease, and TS could be considered a hyperkinetic state. Interestingly, DBS in both the motor and limbic areas of GPi have been described separately. In 2003, Diederich

et al.,[17] a group in Vienna, published a case of bilateral DBS in the posteroventrolateral motor area of GPi in a 27-year old patient with severe motor and vocal tics. The target and stimulation parameters are shown in Table 1. The authors did not note what part of the electrode array was placed at the target coordinates (tip, contact 0, etc.). Chronic stimulation produced a mean postoperative tic reduction of 73% over a 14-month period. The patient and the evaluators were not blinded. There was a small, apparently asymptomatic hemorrhage at the electrode tip on the right side. No stimulation-induced adverse effects were seen, and cognitive testing in the stimulation on and off conditions were stable at 14 months.

In 2005, a group in Paris published a case of a 36-year old TS patient with comorbid self-injurious behavior with bilateral DBS in both the medial thalamus (Ce and parafascicular nucleus) and the anteromedial limbic area of GPi.[4] Stimulation parameters for both targets are shown separately in Table 1. The patient was placed into a blinded, randomized protocol of thalamic only, pallidal only, combined thalamic and pallidal, and finally sham stimulation. Evaluators were also blinded. After 2 months of limbic GPi stimulation only, the patient showed a decrease in the Yale Global Tic Severity Scale (YGTSS) of 65% and a decrease in the Rush Video Based Tic Scale (RVBTS) of 67%. After 2 months of thalamic stimulation only, the scores were similarly reduced by 65% and 77%, respectively. Simultaneous stimulation of both targets yielded scores reduced by 60% and 77%, respectively. Self-injurious behavior decreased with both targets, although mood and impulsivity improved more with thalamic stimulation. Symptoms returned after a 1-month delay with sham stimulation. The Dutch-Flemish group has also reported on a simultaneously implanted dual target patient, with medial thalamic and motor GPi DBS (Table 1).[18] After 2 weeks of externalized test stimulation with each pair of electrodes separately, the GPi electrode was believed to provide more tic reduction and only these electrodes were stimulated chronically; however, clinical comparison to another patient in the same study with only thalamic DBS showed similar striking tic reduction in either target with both patients and evaluators blinded.

OBSESSIVE-COMPULSIVE DISORDER

OCD is characterized by recurrent obsessive thoughts and compulsive mental or physical acts, usually in response to those obsessions. It can be extremely disabling when refractory to medical therapy, and most surgeons who treat OCD agree that these are among the most difficult patients to treat with surgery. OCD is also frequently comorbid with anxiety and depressive disorders, as well as with TS as previously noted. There is some evidence that OCD and TS are related entities along a disease spectrum, and that the two disorders together are more severe than either one in isolation, which may eventually have implications with regard to patient and target selection.[19] Many investigators who study TS or OCS strive to find patients who have these disorders in isolation for scientific reasons, but this is often a challenge.

The early DBS targets for OCD focused on the region of the internal capsule and ventral striatum. This was largely based on the successful history of lesioning procedures for OCD, which have been well studied and done with some regularity.[20–27] At the ventral end of the internal capsule, rostral to the level of the anterior commissure, is the nucleus accumbens (NAcc), which has been implicated as a potential target in all three of the psychiatric disorders currently treated with DBS.[6,28,29] The "ventral capsule," as its name implies, refers to the ventral portion of the internal capsule, whereas the term "ventral striatum" is meant to include the NAcc. Still others refer to the nucleus accumbens directly. The NAcc is believed to receive afferents from multiple limbic and motor areas, such as the amygdala, orbitofrontal/medial prefrontal cortex, caudate, and pallidum, and it has efferents to multiple mesolimbic and prefrontal areas as well as the cingulate cortex, striatum, pallidum, and thalamus.[30–32] It is important to point out that a DBS lead spanning this region is capable of activating any of these structures, depending on the lead geometry and stimulation parameters used. Finally, subthalamic nucleus (STN) stimulation in Parkinson's patients with co-existent OCD has been implicated as a potential target, and ventral caudate nucleus DBS in one patient showed improvement in both OCD and comorbid major depression.[33–35]

A group from Belgium reported their results on the use of DBS in the anterior limb of the internal capsule (AIC).[6,36] In their 2003 publication, six patients were implanted with widely spaced electrodes (one with Medtronic Model 3487A Pisces leads, five with Model 3887 Pisces leads) such that the middle two contacts were in the region that would normally be targeted for an anterior capsulotomy. Interestingly, this placed the most ventral contact in or near the NAcc. All patients entered a screening phase for several weeks to several months after surgery to determine optimal stimulation parameters. One patient experienced limited benefit, but he required such high stimulation settings that his pulse generator only lasted 5 months; his electrodes were removed and he underwent a bilateral capsulotomy. Another patient was still in the screening phase at the time of initial publication. The remaining four patients went on to a blinded, crossover evaluation phase. Table 2 shows the target coordinates that were only given for the patient with the most clinical improvement, along with the stimulation parameters for the other patients. Two other pa-

TABLE 2. *Stimulation Parameters for Reviewed Studies in Obsessive-Compulsive Disorder*

Target	Author	AC-PC Coordinates	Patient	Side	Contacts	Amp (v)	PW (microsec)	Frequency (Hz)
AIC	Nuttin et al. [6]	Not given	2	R	0+ 1- 2+	9	210	100
				L	0+ 1- 2+	9	210	100
		Lat = 13* AP = 3.5*† Vert = 0*	3	R	0- 1- 2- 3- C+	4	210	100
		Lat = 14* AP = 3.5*† Vert = 0*		L	0- 1- 2- 3- C+	4	210	100
		Not given	4	R	1- 2+	10.5	450	100
				L	1- 2+	10.5	450	100
		Not given	6	R	Unclear	7	200‡	100
				L	Unclear	7	200‡	100
	Abelson et al. [5]	Lat = 10.7 AP = 5.9† Vert = -1.4	3	R	0- C+	7	210	130
		Lat = 11.4 AP = 6.8† Vert = -1.8		L	0- C+	7	210	130
VC/VS	Greenberg et al. [39]	(See text)						
STN	Mallet et al. [35]	Not given	1	Unclear§	Unclear‖	3.1	60	185
		Not given	2	Unclear§	Unclear‖	3.2	90	130
	Fontaine et al. [33]	Lat = 12.5 AP = -0.6¶ Vert = -1.5	1	R	"Monopolar"#	3.5	60	185
		Lat = 10 AP = -3.8** Vert = -4.8		L	"Monopolar"#	1.3	60	185

AC = anterior commissure; AIC = anterior limb of the internal capsule; AP = anterior-posterior; L = left; Lat = lateral; MCP = midcommissural point; PC = posterior commissure; PW = pulse width; R = right; STN = subthalamic nucleus; v = volts; Vert = vertical; VC/VS = vertical capsule/ventral striatum.
*Coordinates are for "middle of electrode tip." †Anterior to the posterior margin of the AC. ‡Reported as 200, but this is an unusual value for PW; likely meant to be 210. §Only described as "bilateral stimulation." ‖Contacts reported as "anterolateral STN" and "zona incerta", but unclear if one or both used, monopolar or bipolar. ¶Reported as 13.4 anterior to PC; AC-PC distance = 28, so AP = -0.6 from MCP. #AC-PC coordinates given are for the "active contact"; not specified exactly which contact. **Reported as 10.2 anterior to PC; AC-PC distance = 28, so AP = -3.8 from MCP.

tients formally enrolled and two anecdotal patients were discussed in an addendum to the article on this report.[6]

Standard criteria for a significant clinical response in OCD are a 25 to 35% reduction in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The initial four patients entering the crossover phase were considered to be responders, experiencing at least a 35% reduction in Y-BOCS scores in the stimulation on state.[6] The mean Y-BOCS score with stimulation was 19.8 ± 8.0; the mean score without stimulation was 32.3 ± 3.9. One of the most interesting aspects of the study was the relatively high stimulation parameters that were necessary for optimal benefit. In DBS, the clinical effect is believed to be centered around the negative (cathodal) contact or contacts. Two patients had only one negative contact, but one had three negative contacts, and the other had four negative contacts, indicating that a large area of the target region required stimulation. The amplitudes in patients with only one negative contact were 9.0 v and 10.5 v (the maximum voltage delivered by the system), and the others were 5.5 v and 4 v. Pulse widths were also fairly high (210–450 microseconds).

These parameters are significant for several reasons. From a practical standpoint, pulse generators do not last long with high stimulation settings. The initial four patients entering the blinded phase of this study required battery replacements every 5 to 12 months.[6] From a conceptual standpoint, many believe that the further away from the target an electrode is, the higher the levels of stimulation that will be required to produce the desired clinical effect; this is commonly seen in the targets used for movement disorders. It is not known if this concept is applicable in the context of OCD and capsular stimulation; on a broader scale, the exact mechanisms of DBS itself are not known.[37]

The authors of the article recognized the limitations of limited battery life, and in the addendum to the article they describe a fifth patient who entered into the cross-

over phase with DBS in both the AIC and magnocellular portion of the dorsomedial nucleus (DM) of the thalamus.[6] The intent was to find a "better" target from a battery life standpoint; selection of the DM as a target was based on a prior lesioning study by Spiegel et al.[38] Again, specific stereotactic coordinates were not given. The patient was ultimately found to be a nonresponder to stimulation in either target, and no details were given regarding the stimulation parameters other than the active contacts used. The sixth patient was a responder, but he became severely obsessive and suicidal with blinded cessation of stimulation; this patient was removed from the blinded phase of the study.

A similar study was performed in Michigan with four patients who were also implanted in the traditional anterior capsulotomy target.[5] The more common Medtronic Model 3387 leads were placed, again with the electrode tip targeted at the bottom of the capsule at the junction of the NAcc. Although initial target coordinates were not given, two of the four patients underwent postoperative MRI lead location analysis. A single cathodal contact was used as the most ventral end of the lead. Only one patient (number 3) was considered a responder, with a reduction in Y-BOCS of 67% under blinded stimulation conditions (Table 2). High levels of stimulation were also needed in this study, with the one responder requiring 7.0 v and needing a new pulse generator every 10 months during the follow-up period. An apparent exacerbation of depressive symptoms after loss of stimulation and a lead fracture was also seen in this patient, adding to concerns other investigators have had over short battery life and sudden cessation of therapy in this patient population.[5,39]

Others have explored the ventral region of the capsule and the accumbens in an effort to find a more effective target. Several groups have made the observation that lesions made more ventral in the AIC are more clinically effective, and that the high stimulation levels and use of ventral negative contacts in the study from Belgium might be stimulating the NAcc.[21,39] A collaborative effort between several centers in the United States published studies with 10 patients implanted in the ventral capsule/ventral striatum (VC/VS).[39] No specific stereotactic coordinates were reported, but the electrodes were placed such that the ventral-most contact "extended into the ventral striatum, in the caudal nucleus accumbens".[39] Stimulation parameters were reported across patients instead of individually, so they will be summarized here instead of in Table 2. Amplitudes were reported in a milliamp, which is calculated based on the measured electrode impedance at a specific voltage. Amplitudes were between 8 and 17 milliamps, with pulse widths of 90 to 210 microseconds and frequencies of 100 to 130 Hz. The most ventral contact was negative in 8 of 10 patients. The second and third most ventral contacts were negative in 7 of 10 and 3 of 10 patients, respectively. Although all patients were implanted bilaterally, two patients were only stimulated unilaterally (one right and one left). The mean pre-surgical Y-BOCS score was 34.6 $\pm$ 0.6. The mean postoperative score was 22.3 $\pm$ 2.1. By 36 months follow-up, one patient had died of breast cancer and another was only at 24 months follow-up. Of 8 patients at 36 months, 2 patients were nonresponders (improvement in Y-BOCS $<$ 25%), two were responders with Y-BOCS improvement between 25 and 35%, and four had outstanding responses with improvement well over 35%. A German group has also published a series of four patients with active contacts in the NAcc; in their series, only right NAcc stimulation was believed to provide clinical benefit.[21] Three of the patients were reported to have "nearly total recovery from both anxiety- and OCD-symptoms without any side effects," but unfortunately no clinical outcomes measures of any kind were included.

Finally, a pair of articles from France illustrates a nice example of a target discovered fortuitously. Three patients total with medically refractory Parkinson's disease were treated with DBS in the region of the subthalamic nucleus. The patients also happened to have a long-standing history of OCD. In the 2002 series from Paris, two patients were found to have a striking reduction in their Y-BOCS scores (81% and 83%) after unblinded stimulation (Table 2).[35] The authors noted that the active contacts resulting in this clinical effect were more medial than expected in the STN. Although the effect may be the result of stimulation of adjacent structures, they theorized that the changes seen were mediated by the STN itself. In a separate case report from Nice in 2004, STN stimulation at the parameters shown in Table 2 led to a 96.9% reduction in Y-BOCS score, again with unblinded stimulation.[33] The authors believe that the site of effective stimulation was either in the STN or just above it in the zona incerta or the fields of Forel. This work has led to a multicenter French study of STN DBS for OCD that is currently ongoing.

TREATMENT-RESISTANT DEPRESSION

Major depression is by far the most common psychiatric disorder worldwide. Up to 20% of patients that carry major depression as a formal diagnosis fail to respond to traditional pharmacotherapy, and must undergo treatment with multiple agents and/or electroconvulsive therapy.[40,41] It is frequently comorbid with other psychiatric disorders, and by itself is a leading cause of disability (as well as death) worldwide. The targets for depression have been the least explored to date, yet far more effort is being placed on advancing the use of DBS in this disease, driven in part by researchers because of clinical need and in part be-

TABLE 3. *Stimulation Parameters for Reviewed Studies in Treatment-Resistant Depression*

Target	Author	AC-PC Coordinates	Patient	Side	Contacts	Amp (v)	PW (microsec)	Frequency (Hz)
Cg25	Mayberg et al. [8]	Not given*	1-6†	Not given	Not given	4†	60†	130†
NAcc	Schlaepfer et al. [45]	Not given‡	1-3§	Bilateral§	0- 1- C+§	4§	90§	145§

AC = anterior commissure; Cg25 = subgenual cingulated "area 25" NAcc = nucleus accumbens; PC = posterior commissure; PW = pulse width; v = volts.
*See text for description of targeting. †Mean stimulation parameters given for all six patients, includes two long-term nonresponders. ‡Contact locations given as most ventral in shell of NAcc, with second most ventral in core of NAcc. §All patients apparently had identical parameters bilaterally.

cause of device companies. Both are motivated by the relatively large numbers of patients that could be helped with this therapy.

The group from Toronto published the largest series of the use of DBS for TRD to date.[8] This study is a very nice example of the potential of neuroimaging alone to find new targets for DBS, something that has not been common, but will likely become a significant means of target selection in the future.[42] The study was based on positron emission tomographic findings in symptomatic and successfully treated patients with depression in an area of the interior frontal lobe, the subgenual cingulate (Cg25 or "area 25"). A decrease in Cg25 activity is associated with clinical improvement using multiple treatment modalities for depression including medical therapy, electroconvulsive therapy, transcranial magnetic stimulation, and ablative surgery. An extension of these observations was to attempt to modulate the activity of Cg25 directly by DBS.[8,43,44]

Six patients were implanted with bilateral Medtronic 3387 leads in the Cg25. Specific stereotactic coordinates were not given; however, this target is somewhat unique as it is a gyrus, not a nuclear structure, and a detailed methodology for targeting was described. A coronal T2 image was obtained at the midpoint between the most anterior surface of the genu of the corpus callosum and the anterior commissure; the transition point from gray matter to white matter in Cg25 on this slice was then used as the target. Information regarding the specific active contacts used for chronic stimulation was not given. The authors did report that the average stimulation settings for the group were 4.0 v, pulse width of 60, and 130 Hz, although this presumably includes two patients who were nonresponders at the 6-month time point. These averaged group data are reflected in Table 3. Individual stimulation parameters were only given for one patient, who had the best and earliest clinical response and who was placed in a blinded stimulation paradigm. Her settings were 3.5 v, pulse width of 60, 130 Hz, with unknown active contacts. At one month postoperatively, two of the six patients met the criteria for clinical response, which were defined at a decrease in the Hamilton Depression Rating Scale (HRDS-17, also known as HAM-D) of 50% or more from the pretreatment baseline. At two months, five of the six patients met the criteria for response, although in one patient this would not be sustained. At the 6-month endpoint, four of the six patients had continued benefit. Two of the patients developed persistent wound infections; fortunately, these happened to be the nonresponders at 6 months, and both were therefore explanted with resolution of their infections. A third patient developed an erosion over the hardware but this was successfully treated with antibiotics. No stimulation-related adverse effects were seen.

The VC/VS and NAcc region has also been described as a target for TRD. A German group[45] in 2007 published studies of a series of three patients implanted in the ventral striatum. They cited several reasons for using this target. First, the NAcc is a region involved in processing reward and pleasure, which they believe is dysfunctional in depressed patients. In addition, this region is a gateway between limbic areas of the brain and motor areas of the brain, and it is in a central, unique position to modulate activity in many other upstream and downstream regions. Three patients were implanted bilaterally with the contacts located in the shell of the NAcc, the core of the NAcc, and in the ventral internal capsule. No anterior commissure-posterior commissure coordinates were given. The stimulation parameters are shown in Table 3. A double-blind stimulation paradigm was used. The baseline Hamilton Depression Rating Scale average was 33.7 ± 3.8. After only one week of stimulation, the average dropped to 19.7 ± 6.7. After one week of blinded withdrawal of stimulation, the average rose again to 29.3 ± 5.5. Other clinical measures followed the same pattern. The return of symptoms after withdrawal of stimulation was so severe in two of the patients (who incidentally happened to be monozygotic twins) that the placebo stimulation period was cut short. No negative side effects were reported. Encouraging preliminary results in the VC/VS region were also reported by an Amer-

ican group at the American Association of Neurological Surgeons in 2006.[29]

DISCUSSION

Many comments have been made about the need to avoid repeating the mistakes made in the past with psychosurgery. Although this is good advice, the environment today is quite different than it was more than half a century ago, and in the age of DBS there are new mistakes to be made. We must study the potential for DBS with scientific rigor, open-mindedness, and responsibility to our patients and the public.

The preliminary work reviewed here does have its limitations. The sample sizes are low, and the issue of blinding is a challenge because the effects of stimulation (or withdrawal of stimulation) may be perceptible by the patient or even dangerous if severe rebound symptoms occur.[3,5,6] Because the number of patients is so small, and the cases are being done at centers scattered around the world, it is critical that as much information as possible regarding target coordinates, lead location, and stimulation parameters be included in publications. In addition, investigators should use standardized clinical rating scales to quantify patient responses to therapy. It is very hard in the current era to justify not including such data when reporting patient outcomes.

It is encouraging to see that multidisciplinary groups have formed to create published statements regarding issues such as patient selection, inclusion/exclusion criteria, preoperative and postoperative evaluations, and target selection for TS and OCD.[22,27,46] This proactive effort is useful and welcome. It also begins to address the concern that DBS surgery for psychiatric disorders may be adopted too casually by some clinicians. DBS seems "safer" than lesioning procedures, and many neurosurgeons are comfortable with this modality. However, the psychiatric population and the disorders they suffer from are very different than patients with movement disorders, and the clinical and surgical needs of the psychiatric patient are unique. They require the involvement of an experienced, dedicated psychiatrist and an experienced surgical team, with a commitment to rigorous data collection and the intent to share their techniques and results, positive or negative, with the medical community.

It is important not to become too dogmatic in target selection at the present time. Movement disorders surgery has taught us that basal ganglia disorders can benefit from neuromodulation at multiple sites; a quick glance at the studies reviewed here would suggest the same may be true in TS, OCD and TRD. There is convincing and converging evidence that there are loops involving limbic, basal ganglia and cortical areas underlying these disorders, which would further support the concept of efficacy at multiple targets.[47–52] It is important to move forward with an open mind, and report data carefully such that meaningful comparison of targets can be made.

Finally, DBS is a dramatic therapy to see in action, and the patients suffering from these disorders, their families, and the public are very impressionable and anxious for a "cure." The increasing national interest in DBS for psychiatric disorders has led to coverage by several prime-time television programs in the United States, which are sometimes capable of portraying our knowledge of these disorders in a very favorable and confident light, despite our efforts to be objective. The truth, of course, is that our knowledge regarding the use of DBS in these patients is extremely preliminary, and we in this specialty must continue to be careful and sometimes wary about how the lay press disseminates information to the public.

CONCLUSIONS

The studies to date indicate that the future of DBS in psychosurgery has significant promise. The multitude of targets explored, as well as overlap of targets for DBS between TS, OCD, and TRD, contribute to the growing concept that these conditions have a strong component involving the limbic and, perhaps, motor areas of the basal ganglia. Given this, and considering the parallels with the evolution of movement disorders surgery over the last decade, the term "limbic disorders surgery" may be a more appropriate name for this rapidly evolving and exciting specialty. DBS is certainly contributing greatly to our knowledge and potential treatment of these disorders, and will likely continue to do so in the years to come.

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